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A Comparative Study of Topical Voriconazole and Topical Natamycin in Patients with Fungal Corneal Ulcers - A Clinical Study in a Tertiary Care Hospital

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Abstract: ***Introduction: Infectious corneal ulcers of fungal origin affecting people of tropical and developing countries is one of the leading cause of blindness .Fungi are present in fresh or decaying organic matters, paddy leaves, cow tail, agricultural vegetative remnants. Management of fungal corneal ulcer requires timely diagnosis and administration of appropriate antifungal therapy. Aim. : To evaluate the efficacy of topical 1% voriconazole versus 5% natamycin in the treatment of fungal corneal ulcers. Materials and Methods: The present study entitled- A comparative study of topical voriconazole and topical natamycin in patients with fungal corneal ulcers- A clinical study in a tertiary care hospital was carried out in the Department of Ophthalmology, Fakhruddin Ali Ahmed Medical college, Barpeta, Assam from JAN 2019 to Dec 2019.A total number of 40 patients with microbiologically proven fungal corneal ulcers were taken for the study. Results: Two groups of 20 patients of fungal corneal ulcers were started on treatment with either 1%voriconazole or 5% Natamycin.Corneal ulcer healed in 17 (85%) of 20 patients in voriconazole treated group and in 18 (90%) of 20 patients of natamycin treated group. There was no significant statistical differences between the two groups (P=1.00). Conclusions: success rate of both the drugs were comparable and voriconazole therapy did not show any additional beneficial effect over natamycin.***

Keywords: Fungal corneal ulcer, Voriconazole, Natamycin

1. Introduction

Corneal diseases are one of the major causes of vision loss and blindness .Ocular trauma and corneal ulceration results in new cases of corneal blindness annually. Fungal corneal ulcer is more common in tropical region as well as in developing countries like India, constituting 44% to 59% of all corneal ulcers[1].Ocular morbidity in fungal infection is greater than bacterial keratitis because of delayed diagnosis and availability of drugs are not very effective. Fungi are present in fresh or decaying organic matters, paddy leaves, cow tail and other agricultural vegetative remnants. Injury caused by these objects predisposes cornea to fungal invasion. Management of fungal corneal ulcer includes timely diagnosis of the infection and administration of appropriate antifungal therapy. Among variety of antifungal therapy in our study we use topical voriconazole (1%) and topical natamycin (5%) eye drops. Assam is located in semitropical region. Its climatic condition is humid and moist with rainfall which is favourable for growth of fungi. In this study efficacy of topical 1% voriconazole and topical 5% natamycin in the treatment of fungal corneal ulcer was compared.

2. Review of Literature

Theoder Leber reported first case of fungal infection of cornea in 1879, involving a farmer who was stuck in the eye by oat chaff with resultant keratomycosis caused by Aspergillus glaucus[2]. Leber (1879) uses combination of curettage and chemical cautery with carbolic acid to cure.

Fungal infection occurs all over the world but the incidence is highest in warm and humid climates and particularly in rural environment. Fungi are ubiquitous, saprophytic and /or pathogenic organisms. Saprophytic fungi obtain their nutrients from decaying organic matter, whereas pathogenic fungi feeds on living cells.

Fungi isolates in the ophthalmic literature includes

1) Yeast which includes candida spp.
2) Filamentous septate fungi, which includes -a.non pigmented hyphae (Fusarium spp and Aspergillus spp) b.pigmented hyphae (Alternaria spp and Curvularia spp).
3) Filamentous non septate fungi, which includes mucor spp
4) Other fungi.

The organisms most commonly found in healthy eyes includes Aspergillus spp., candida spp., Cladosporium spp., rhodotorula spp., and Alternaria spp.

Risk factors of fungal corneal ulcer includes--
Trauma, contact lens wear, topical therapy with antibiotics and corticosteroids, topical anaesthetic abuse, coexisting ocular disease-dacryocystitis, lid abnormalities, herpes simplex infection, lagophthalmos etc.

Pathogenesis of fungal corneal ulcers- intact corneal epithelial surface with its tight junctions formed by desmosomes and demidesmosomes is the main line of defence against microbial infection. Breach of the epithelial barrier is often a prerequisite for corneal ulcer.

Clinical features of fungal corneal ulcers-The early diagnosis of fungal corneal ulcer is aided by a high index of clinical suspicion and the presence of suggestive finding on

slit lamp biomicroscopy. Non specific clinical features includes-conjunctival ingestion, epithelial defect, anterior chamber reaction etc. Specific clinical features – corneal infiltrate, feathery margin, satellite lesions, elevated edges, rough texture etc.

Laboratory diagnosis-Laboratory investigation of a suspected fungal corneal ulcer begins with the collection of appropriate specimen, which are subjected to microscopic examination, culture, histological testing, or other investigations. Examinations of the corneal scraping done.

Direct microscopic examination of the fungi- 1.Grams stain 2.Giemsa stain 3.10% Potassium hydroxide preparation 4.Gomori methenamine silver (GMS) stain 5.Fluorescent microscopy 6.Lactophenol cotton blue (LCB) staining.

Culture-Commonly used culture media include Sabourauds dextrose agar, blood agar preferably sheep blood agar, chocolate agar and thioglycolate broth .

Corneal biopsy-indicated in corneal ulcers not responding to treatment.

Other investigations includes anterior chamber tap and PCR.

Treatment-Before 1969, most cases of fungal corneal ulcers were treated with topical Amphotericin B. Subsequently polyene natamycin was used. From 1979 natamycin used for topical ocular use. Different antifungal drugs includes - a.Polyenes-Amphotericin B, Natamycin. b.Azoles-econazole, miconazole, ketoconazole, fluconazole, itraconazole, voriconazole.c-Pyrimidines-5-fluorocytosine.d-Allylamines-Terbinafines. e-Echinocandins-caspofungin, micafungin

Natamycin is a broad spectrum antifungal drug activity against various fungi including species of Fusarium, Aspergillus, Acremonium, penicillium, lasiodiplodia and candida. It is stable in 5% suspension. Its topical ophthalmic suspension is well tolerated and causes no pain or secondary corneal damage.It has poor penetration into deeper structurs of the eye and hence, is generally effective against superficial infections that are not severe[3].

Voriconazole is a more recent azole antifungal.Voriconazole have a broad spectrum activity against aspergillus spp., cryptococcus neoformans, scedosporium spp., curvularia spp., Paecilomyces lilacinus and others[4].Topical voriconazole eye drops, manufactured extemporaneously and used in an off-label manner. With topical administration, voriconazole demonstrated good penetration through the cornea into the aquous humour[5].

Duration of treatment-a prolonged period of treatment upto 4-6 weeks is usually needed in the best circumstances and in some instances an even longer period is necessary .Signs of improvement of fungal corneal ulcer are decreased size of corneal infiltration, disappearance of satellite lesions and rounding out feathery margins. Conjunctival ingestion and chemosis often results from antifungal drugs, so their presence or absence cannot be used as an indication of the success of therapy.

Debridement-done with spatula or blade at the slit lamp under topical anesthesia in an interval of 24 to 48 hrs. Which works by debulking organisms and necrotic material and enhances the penetration of the topical drugs.

Therapeutic keratoplasty-indicated in a-progression of infection despite pharmacological treatment. b-impending or actual perforation. C-progression of infection to involve limbus and adjacent sclera.

3. Materials and Methods

This study was conducted in the Department of ophthalmology, Fakhruddin Ali Ahmed medical college and Hospital, Barpeta, Assam during the period from Jan 2019 to Dec 2019.The study was conducted after seeking ethical clearance from the institutional ethics committee. The patients were selected from outdoor as well of indoor of Department of ophthalmology, F A A Medical College, Barpeta, Assam who were microbiologically proven fungal corneal ulcer.

Inclusion criteria-* Cases of fungal corneal ulcer (evidence of fungal elements on KOH mount and /or culture positive) attending F A A Medical College and Hospital, Barpeta. *Age more than 16 years. Exclusion criteria- *Impending perforation. *bilateral ulcer *already taking antifungal drugs at the time of presentation.*evidence of significant bacteria on gram stain at the time of presentation . *known allergy to the study medications *no light perception on the affected eye.

Sample size-40 patients satisfying above criteria were selected from the study population.

After taking informed consent, a detailed history was taken. General and systemic examination was done. Ocular examination included recording of visual acuity with snellens chart, detailed slit lamp examination of the corneal ulcer including measurement of the size of epithelial defect, depth of stromal infiltrate and hypopyon. Fluorescein staining of ulcer and lacrimal sac syringing was performed.All the findings of the history and ocular examination were recorded in a pre designed proforma. Documentation of relevant findings was made in the form of photography. Sample collection-Once clinical diagnosis of corneal ulcer was made, corneal scrapping were taking by aaplying topical anaesthesia (4% lignocaine or 0.5% proparacaine solution) with sterile bard parker blade (no.15) under slit lamp. The following microbiological investigations were done-

Direct microscopy- *Direct 10% potassium hydroxide (KOH) wet mount * Gram stain

Culture-* Sabourauds dextrose agar with chloramphenicol (50bmg/ml) *Blood agar *Chocolate agar *Potato dextrose agar (for slide culture)

Treatment: Patients were randomly assigned into two groups. Group A- received topical voriconazole 1% eye drops hourly. Vozole (Aurolab, Madurai, India) contains 30 mg sterile lyophilized dry voriconazole powder. To get 1%

(10 mg/ml0 solution, this powder has to be reconstituted with 3ml of water for injection. Group B-received topical natamycin 5% eyedrops hourly. One drop of medication was applied 1 hrly while awake to the affected eye for 1 week and then every 2 hrly while awake until 2 weeks. Further doses was titrated according to the patients response. In addition, patients were started on topical atropine sulphate 1% eye drop 3 times daily, moxifloxacin 0.5% eye drop 4 times daily, 0.5% timolol maleate eye drops twice daily if needed and systemic analgesics. Patients were scheduled to followed up every day for 1 week. Subsequently every third day for 2 weeks, then every week for 12 weeks or complete resolution of infiltrate whichever was later.

Analysis of the results was performed using standard statistical methods.

4. Results and Observations

The following observations were made from the present study. Two groups of patients who were microbiologically proven fungal corneal ulcers were started on treatment with either 1% voriconazole or 5% natamycin eye drops.

1) Age distribution

Age in years	Voriconazole group	Natamycin group	Total	Percentage
16-30	5 (25%)	6 (30%)	11	27.5%
31-40	7 (35%)	6 (30%)	13	32.5%
41-50	3 (15%)	3 (15%)	6	15%
51-60	4 (20%)	3 (15%)	7	17.5%
≥61	1 (5%)	2 (10%)	3	7.5%

Maximum no of cases occurred in the age group of 31-40 years.Fungal corneal ulcer was least in the age group ≥61years.

2) Sex distribution in two groups

Sex	Voriconazole group	Natamycin group	Total
Male	11	14	25 (62.5%)
Female	9	6	1537.5%)

3) Distribution with respect to occupation of patients in two groups

Occupation	Voriconazole group	Natamycin group	Total
Farmers	7	9	16 (40%)
Labourers	6	3	9 (22.5%)
Housewives	5	3	8 (20%)
carpenter	1	2	3 (7.5%)
Trademan	1	1	2 (5%)
others	0	2	2 (5%)

Above table shows that most of the patients were farmers (40%) by occupation, followed by labourers who do outdoor works (22.5%), housewives (20%), carpenter (7.5%), trademan (5%) .other category included one driver and one retired person each.

4) Distributions of trauma causing agents in two groups

Trauma causing agents	Voriconazole group	Natamycin group	Total
Bamboo stick	5	8	13 (32.5%)
Paddy leaf	7	3	10 (25%)
Hay	2	3	5 (12.5%)
Animal tail	1	2	3 (7.5%)
Soil or mud	2	1	3 (7.5%)
Insect	2	1	3 (7.5%)
No h/o trauma	1	2	3 (7.5%)

Above table shows that history of trauma was present in 37 (92.5%) cases. Bamboo stick (32.5%) was the most common traumatic agent followed by paddy leaf (25%), hay (12.5%), animal tail (7.5%), soil (7.5%), insect (7.5%).

5) Distribution of fungal species isolated

Fungus isolated	Voriconazole group	Natamycin group	Total
Fusarium	4	3	7 (17.5%)
Curvularia lunata	3	4	7 (17.5%)
Aspergillus species	2	3	5 (12.5%)
Sterile hyphae	2	2	4 (10%)
Candida albicans	1	2	3 (7.5%)
Penicillium species	1	1	2 (5%)
No growth of fungi *	7	5	12 (30%)

*These ulcers were smear positive for fungi but culture negative.

The above table shows that fungal culture was positive in 28 (70%) of KOH positive (fungal elements seen) patients. Most common isolates of culture positive cases were Fusarium species (7 pts) and Curvularia lunata species (7 pts) followed by Aspergillus species (5 pts) and candida albicans (3 pts).Sterile hyphae (4 pts) and penicillium species (2 pts).

Clinical Effects

1) Success Rate Between Two Groups

Results	Voriconazole Group	Natamycin Group
Healed	17 (85%)	18 (90%)
Not healed	3 (15%)	2 (10%)
Total	20 (100%)	20 (100%)

The above table shows that corneal ulcer healed in 17 (85%) of 20 patients in voriconazole treated group and in 18 (90%) of 20 patients of natamycin treated group. There was no significant statistical difference between two groups P =1.00.

2) Mean time for resolution of ulcer in both the group

	Voriconazole group (n=17)	Natamycin group (n=18)
Mean time of resolution (days)	30.29	29.44
SD (days)	6.30	4.94

The above table shows that in patients who responded to therapy, the mean time of resolution of ulcers was30.29±6.30 days (range=20 to 44 days) in Voriconazole treated group and 29.44±4.94 days (range=23 to 40 days) in

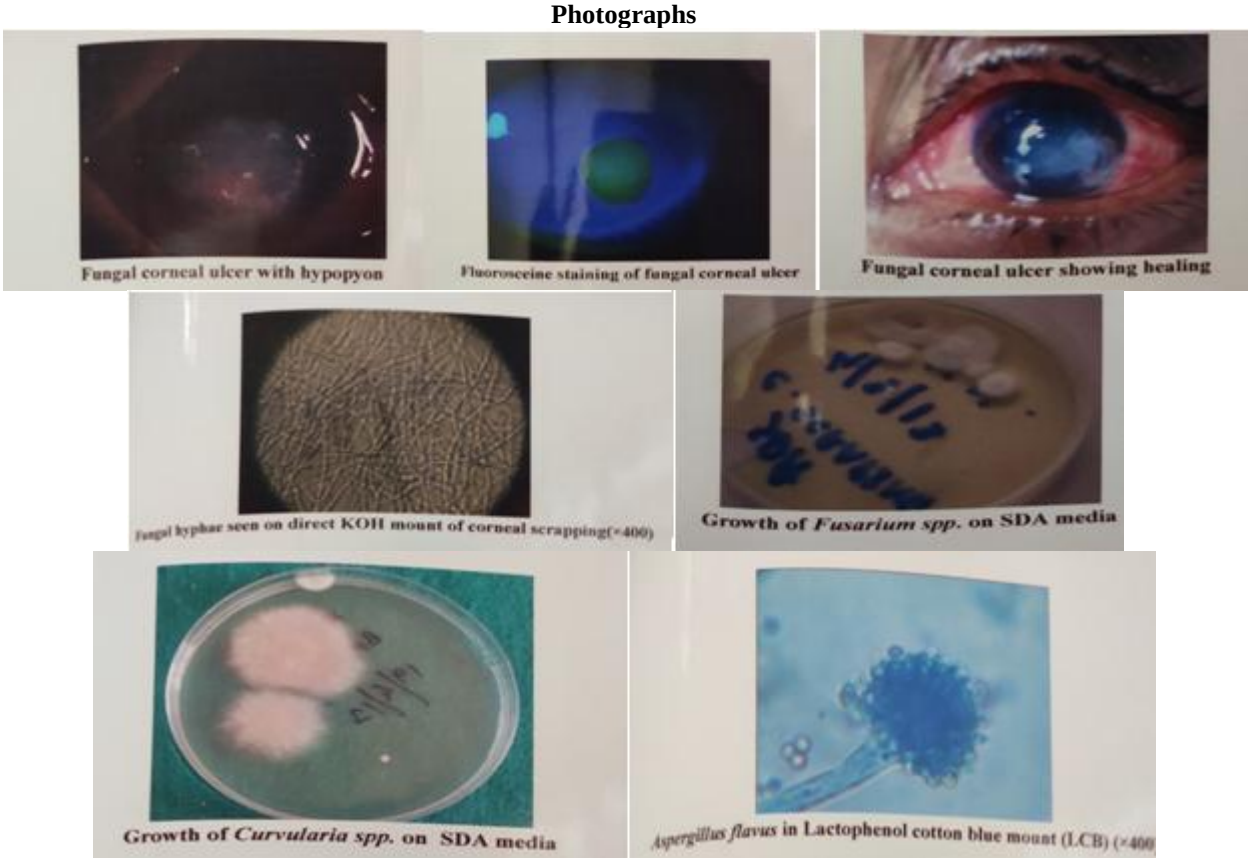
Natamycin treated group. This difference was not significant statistically (P=0.659).

3) Mean best corrected visual acuity (BCVA) in both the group who responed to treatment

Groups	BCVA at presentation	BCVA at 1st week	BCVA at 2 nd week	BCVA at 4th weeks	BCVA at 8 th weeks	BCVA at 12 weeks
Voriconazole group (n=17)	2.09±0.73	1.99±0.82	1.72±0.68	1.41±0.37	1.13±0.29	0.96±0.17
Natamycin group (n=18)	2.21±0.67	1.93±0.63	1.56±0.43	1.30±0.27	1.09±0.25	0.91±0.19

The above table shows the mean best corrected visual acuity (BCVA) at presentation and subsequent follow up to 12 weeks. At 12 weeks BCVA in Voriconazole group was 0.96±0.17 and Natamycin group was 0.91±0.19. The difference being insignificant statistically (P=0.418).

Photographs



5. Discussion

In the present study, 40 patients of fungal corneal ulcers were taked and attempt was taken to study various characteristics of the disease and efficacy of topical 1% Voriconazole was compared with topical 5% Natamycin in the primary treatment of fungal corneal ulcers. Patients were randomized into two groups of 20 each and were started on treatment with either topical 1% Voriconazole or topical 5% Natamycin eye drops.

Baseline Characteristics

Age-

In the present study, maximum numbers of cases were in the age group of 31-40 (32.5%), followed by 16-30 years (27.5%). This tallies with study by Chowdhury A et al[6]who reported most cases (37%) of keratitis in the age group of 31-40 years, followed by 31% cases in the age group 21-30 years. Nath et al[75] reported the commonest age group of affected patients to be 41-50 years. This study shows preponderance of the disease in 16-40 years.

Sex

In the present study out of 40 cases, 25 (62.5%) were male and 15 (37.5) were female. This is in accordance with study conducted by Nath et al [7] and Gopinathan U et al [8].

By the nature of their work profile men are more exposed to outdoor activities thereby increasing their vulnerability to the ocular trauma which is major risk factor for fungal corneal ulcer.

Occupation-

In the present study, most of the patients were farmer 16 (40%) by occupation, followed by labourers 9 (22.5%), housewives 8 (20%), carpenter 3 (7.5%), trademan 2 (5%) in that order.One patient was retired and another driver. In the

study, Nath et al [7] 56.7% patients were tea garden workers and 43.3% patients were rice field workers. Bharathi et al[9] reported majority of the patients 64.75% were farmers in their study. People engaged in agricultural activities are prone for injuries with vegetative matter which is associated with higher incidence of fungal corneal ulcer.

Agents causing trauma

Out of 40 patients, history of trauma was given by 37 (92.5%) of them.Bamboo stick 32.5% was the most common traumatic agents followed by paddy leaf 25%, hay 12.5%, animal tail 7.5%, soil 7.5%, insect 7.5% .

Bharathi et al [9] identified corneal trauma 92.15% as the predominant predisposing factor in causing fungal keratitis . Corneal injury with vegetative matter was present in 61.28% patients.

Nath et al [7] found ocular trauma associated with 74.4% cases, most common trauma causing agent was plant matter including 47.9% by leaf, 9.3% by stem and 29.3% by hay.

Predominant occupation in this region is related to agricultural activities, exposing people to traumatic eye injury with vegetative matter and hence to fungal corneal ulcer.

Fungal species isolated

In this study 28 (70%) out of 40 patients were fungal culture positive. Most common isolates of culture positive cases were Fusarium species 7 cases (25%) and Curvularia lunata species 7 cases (25%) followed by Aspergillus species 5 cases (17.8%) and candida albicans 3 cases (10.7%), Sterile hyphae 4 cases (14.3%) and penicillium species 2 cases (5%) .

Studies of Nath et al [7] and Bharathi et al [9] reported similar finding .

Study	Isolates (%)
Nath et al [7]	Fusarium spp 25 Aspergillus spp. 19 Curvularia spp. 18.5 Penicillium spp. 15.2 Sterile hyphae 3.8
Bharathi et al 9	Fusarium spp.42.82 Aspergillus spp. 26
Present study	Fusarium spp 25 Curvularia spp 25 Aspergillus spp.17.8 Candida spp 10.7

Clinical Effects

Success Rate

Corneal ulcer healed in 17 (85%) of 20 patients in Voriconazole treated group and 18 (90%) of 20 patients Natamycin treated group. Arora R et al [10] reports 93% success rate with topical 1% voriconazole and 100% success rate with 5% natamycin group.

Mean Time of Resolution

The mean time of resolution of ulcers was30.29±6.30 days (range=20 to 44 days) in Voriconazole treated group and 29.44±4.94 days (range=23 to 40 days) in Natamycin treated group. This difference was not significant statistically (P=0.659). In the study of Arora et al[10] reported average time of resolution in 15 patients of Natamycin treated group was 24.33 days and in 14 patients of voriconazole treated group was 27.42 days.

Mean visual acuity at follow ups in both groups

Visual acuity improved in both the Voriconazole and Natamycin treated group. At baseline the mean BCVA in voriconazole group was 2.09±0.73 logMAR and in natamycin group it was 2.21±0.67 logMAR. At 12 weeks, the voriconazole group had a mean BCVA of 0.96±0.17 logMAR. By 12 weeks, the natamycin group exhibited greater improvement with a mean BCVA of 0.91±0.19 logMAR .The difference however was not statistically significant (p=0.418). However in similar study by Prajna et al [11] Voriconazole group (0.63) exhibited greater improvement in compared to Natamycin group (0.69) at 3 months in mean BCVA..

6. Conclusion

In this study, baseline characteristics of fungal corneal ulcer were studied and efficacy of topical 1% Voriconazole was compared with 5% Natamycin eyedrops in primary treatment of fungal corneal ulcers.

Fungal corneal ulcers are more commonly seen in peoples from agricultural background and trauma from vegetative matter is most common associated risk factor.

Fusarium spp and Curvularia spp were the most common species among the culture positive cases in our study.

This study showed no significant difference in final visual acuity with topical 1%Voriconazole and 5% Natamycin eye drops.Though the mean time for resolution of ulcer was marginally longer in Voriconazole treated group than Natamycin treated group, this was not statistically significant.

Success rate of both the drugs was comparable and Voriconazole therapy did not show any additional beneficial effect over Natamycin.

So, we must continue Natamycin eye drop as first line of drug in the primary treatment of Fungal corneal ulcer and Voriconazole as an effective alternative .

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Nil

Conflicts of Interest

There are no conflicts of interest.

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